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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,254	05/07/1999	WOLF-GEORG FORSSMANN	FORSSMANNETA	9824

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EXAMINER	
SODERQUIST, ARLEN	

ART UNIT	PAPER NUMBER
1743	24

DATE MAILED: 12/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/242,254	Forssmann et al.
Examiner	**Art Unit**
Arlen Soderquist	1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 20, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 4-9, and 11-15* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 4-9, and 11-15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 20, 2002 has been entered.

2. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1743, Examiner Soderquist.

3. The disclosure is objected to because of the following informalities: this application needs a reference to the fact that it is a National Stage Application of the international application containing the appropriate application numbers and filing dates.

Appropriate correction is required.

4. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 1 requires that the low molecular weight peptides are detected by MALDI mass spectrometry which is narrower that the limitation of claim 7.

5. Claims 4-5, 8 and 11-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 4 and 5 are dependent from a canceled claim. Additionally it is not clear if claim 4 actually constitutes a further limitation of claim 1 since a group of peptides having a molecular weight up to 30,000 Dalton would inherently include by definition peptides with two amino acid residues (dipeptides) but not single amino acids. In claim 8 it is not clear if the limitation constitutes a further limitation of claim 1 since examiner is not aware of the MALDI mass spectrometric being able to measure anything but the molecular weights of the constituents present in the measured sample. In claim 11 the samples listed appear to be organisms which are not consistent with either the samples (hemofiltrate, ascitic fluid and urine) or organisms (animals and humans) to which claim 1 limits the method. In claim 12 "the

detecting the condition" is not consistent with "detecting a pathogenic or any other condition" as found in the preamble of claim 1. It appears that applicant is trying to claim that through the relating step the overall condition of the organism is examined in order to reveal any deviations from a reference condition. In claim 13 a transformed organism does not appear to be totally within the scope of the organisms of claim 1 or find antecedent basis therein. Claim 14 appears to be missing a step to allow the detection of the low molecular weight proteins. While it is true that a chromatography method such as size exclusion chromatography can allow direct detection of sample components less than the selected size other interactions used to separate molecules in chromatography are not size related or dependent. Additionally most detection methods used in chromatography are not molecular weight sensitive. Thus chromatography does not guarantee that the results obtained will show only molecules having a molecular weight less than a desired cut-off without either removal of the higher molecular weight substances or use of a detection method that is molecular weight sensitive.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claim 14 is rejected under 35 U.S.C. 102(b) as being anticipated by Tellerova, Shibata (JP 55-37944), Mabuchi, Leber or Klosse (all newly cited and applied).

In the paper Tellerova discusses urinary peptides in rheumatic diseases. Hydroxyproline-containing peptides with molecular weights >4000 were separated from the urine of normal subjects and patients with osteoarthrosis and rheumatoid arthritis by reversed-phase high-performance liquid chromatography (HPLC) with UV detection, following fractionation on Bio-Gel P-4 and elution with 0.01M aqueous NaCl. HPLC was carried out on a Separon Si C 18 column and isocratic elution was with phosphate buffer, pH 2.63, containing 25% MeOH. Differences in the chromatography patterns were found not only between controls and osteoarthrosis patients, but also between osteoarthrosis and rheumatoid arthritis patients. The

method could be useful in the treatment of degenerative joint diseases, but further investigations are necessary.

In the abstract of the Shibata patent application is taught that the application teaches glycoproteins and/or glycopeptides for clinical analysis. Nondialyzable, glucose-containing glycoproteins or glycopeptides are isolated from normal urine for use in clinical analysis for the diagnosis of renal disease. Thus, urine (300 L) from normal subjects was concentrated, dialyzed, and freeze dried to give 1 g powdered product. The powder was dissolved in a small amount of water, and the solution was adjusted to pH 8.0 with 0.1M Na borate, treated with 0.5% trypsin at 37° for 3 h and then at 60° for 30 minutes. After centrifugation, the supernatant was dialyzed and freeze dried to produce glycoproteins, which were dissolved in a small amount of saline, and the solution was adjusted to pH 7.4 with 0.1M Tris-acetate buffer. The solution was treated with collagenase and then Pronase, centrifuged, and the supernatant was freeze dried to give glycopeptides. The obtained glycoproteins or glycopeptides were subjected to zone electrophoresis, and the active fractions were eluted and treated with 5% TCA. After removal of the precipitate, the supernatant was desalted and chromatographed on a Bio-Gel P 300 column to give products for use in clinical analysis.

In the paper Mabuchi discusses analysis of small peptides in uremic serum by high-performance liquid chromatography. Peptides from serum samples (samples were ultrafiltered before chromatography, page 292) from 6 uremic patients on maintenance hemodialysis and 4 healthy subjects were analyzed. High-performance gel chromatography showed that peptides with molecular weights below 1,000 were increased in uremic serum; peptides with molecular weights above 1,000 were not increased. Peptides with molecular weights below 1,000 were not detected using ion-pair reversed-phase high-performance liquid chromatography.

In the paper Leber presents studies on the pathogenesis of coma hepaticum; detection of a "middleweight" peptide. Column chromatography of ultrafiltrated serum (hemofiltrate, substances <50,000 daltons) from patients with hepatic coma disclosed an elution peak not present in normal serum. Thin-layer chromatography disclosed that this peak contained 5

middle-molecular-weight peptides. This peak was largely eliminated by 3 hours of hemoperfusion using activated charcoal as an adsorbant.

In the paper Klosse presents an automated chromatographic system for the combined analysis of urinary peptides and amino acids. Column chromatography separation is based partially on the Technicon amino acid analysis NC-1 method. The column eluate is divided into 2 parts, one for peptide analysis using the Folin-Lowry reaction; the other for amino acid analysis with ninhydrin. Peptide and amino acid peak patterns are registered simultaneously in the same chromatogram. Aspecific Folin-Lowry-positive substances, such as phenols and phenolic acids, are removed by EtOAc extraction and macromolecules with a molecular weight above 15,000 by ultrafiltration. Peptide peaks are characterized by relating their position to the positions of the neighboring amino acids. The Folin-Lowry response/ninhydrin response of tyrosine serves as an internal standard for the color yield of the peptide peaks. The peak pattern of normal urines is discussed. Three small groups of patients with tyrosinosis, celiac disease, and bone disorders are also analyzed. Compared with the normals, the excretory patterns of the patients show several differences. Abnormal peptiduria can be thus distinguished and abnormal peptide fractions can be recognized, opening the way for isolation and characterization.

8. Claims 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase (Nippon Iyo Masu Supekutoru Gakkai Koenshu 1992), Kodama or Charpentier (all newly cited and applied).

In the paper Nagase presents analysis of plasma components in uremic hemodialyzed patients by LC/APCI-MS. Peptide containing hydroxyproline was analyzed by a HPLC/atmospheric pressure chemical ionization mass spectrometer. The concentration of prolylhydroxyproline in plasma of uremic hemodialyzed patients was higher in comparison with that of normal subjects. The level was the highest in 2 patients with secondary hyperparathyroidism. The detection of prolylhydroxyproline in plasma of hemodialyzed patients may be useful for the diagnosis of bone resorption.

In the paper Kodama teaches liquid chromatography-mass spectrometry for the qualitative analyses of iminodipeptides in the urine of patients with prolidase deficiency. Analyses of

standard iminodipeptides and iminodipeptides in the urine of patients with prolidase deficiency have been demonstrated using liquid chromatography-mass spectrometry with an atmmospheric pressure ionization interface system. The separation was carried out on a reversed-phase column using 0.1% aqueous trifluoroacetic acid-methanol (70:30 or 80:20). Very intense quasi-molecular ions ([M + H]+) of various standard iminodipeptides were observed by this method. The quasi-molecular ions [M + H]+ of various iminodipeptides (Gly-Pro, Ala-Pro, Val-Pro, Leu-Pro, Ile-Pro, Ser-Pro, Thr-Pro, Glu-Pro, Asp-Pro, His-Pro, Lys-Pro, Pro-Pro, and Tyr-Pro as iminodipeptides containing proline as the C-terminal residue and Glu-Hyp, Pro-Hyp, Ile-Hyp, and Gly-Hyp as iminodipeptides containing hydroxyproline as the C-terminal residue) were identified in the urine of patients with prolidase deficiency.

In the paper Charpentier discusses analysis of dipeptides in urine by gas chromatography/mass spectrometry and the implications for collagen breakdown in iminodipeptiduria following a study of the dipeptides by electron impact and chemical ionization. Dipeptides in the urine of a patient suffering from dermatological purpura associated with iminodipeptiduria were determined by gas chromatography/mass spectrometry as N,O-peracetyl dipeptide Me esters. The dipeptides were identified as R-proline and R'-hydroxyproline were R is any 1 of the residues, glycyl, alanyl, valyl, leucyl, isoleucyl, seryl, aspartyl, glutamyl, prolyl, phenylalanyl and R' is alanyl, valyl, leucyl or isoleucyl, seryl, prolyl, glutamyl, phenylalanyl. The predominance of proline- and hydroxyproline-containing peptide and the percentage distributions of the other amino acid residues, R and R', strongly implicate an abnormality of collagen metabolism. Structural assignments are confidently based on (a) gas chromatographic retention times; (b) electron-impact mass spectra and automatic comparison with reference to spectra stored in a specialized library; © chemical-ionization mass spectra with isobutane and MeOH as reactant gases; and (d) the use of deuterated Ac_2O as derivatizing agent.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

10. Claims 1, 4-9 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tellerova, Shibata, Nagase, Mabuchi, Leber, Kodama, Klosse or Charpentier as applied to claims 14 or 15 above, and further in view of Jimenez or Wang (newly cited and applied). Each of Tellerova, Shibata, Nagase, Mabuchi, Leber, Kodama, Klosse or Charpentier do not teach the use of MALDI mass spectrometry.

In the paper Jimenez teaches neuropeptide expression and processing as revealed by direct matrix-assisted laser desorption ionization mass spectrometry of single neurons. Neuropeptides were directly detected in single identified neurons and the neurohemal area of peptidergic (neuroendocrine) systems in the Lymnaea brain by using matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS). The samples were placed in matrix solution and ruptured to allow mixing of cell contents with the matrix solution. After formation of matrix crystals, the analytes were analyzed by MALDI-MS. It was surprising that clean mass spectra were produced, displaying extreme sensitivity of detection. In one of the neuroendocrine systems studied, the authors could demonstrate for the first time, by comparing the peptide patterns of soma and of neurohemal axon terminals, that processing of the complex prohormone expressed in this system occurs entirely in the soma. In the other system studied, novel peptides could be detected in addition to peptides previously identified by conventional molecular biology and peptide chemistry methods. Thus, complex peptide processing and expression patterns could be predicted that were not detected in earlier studies using conventional methods. As the first MALDI-MS study of direct peptide fingerprinting in the single neuron, these experiments

demonstrate that MALDI-MS forms a new and valuable approach to the study of the synthesis and expression of bioactive peptides, with potential application to single-cell studies in vertebrates, including humans.

In the paper Wang presents the profile of soluble amyloid β protein in cultured cell media relative to detection and quantification of amyloid β protein and variants by immunoprecipitation-mass spectrometry. To study the metabolism of amyloid β protein (Aβ) in Alzheimer's disease, the authors have developed a new approach for analyzing the profile of soluble Aβ and its variants. In the present method, Aβ and its variants are immunoisolated with Aβ-specific monoclonal antibodies. The identities of the Aβ variants are determined by measuring their molecular masses using matrix-assisted laser desorption ionization time-of-flight mass spectrometry. The levels of Aβ variants are determined by their relative peak intensities in mass spectrometric measurements by comparison with internal standards of known identities and concentrations. The authors used this method to examine the Aβ species in conditioned media of mouse neuroblastoma cells transfected with cDNAs encoding wild type or mutant human amyloid precursor protein. In addition to human Aβ-(1-40) and Aβ-(1-42), more than 40 different human Aβ variants were identified. Endogenous murine Aβ and its variants were also identified by this approach. The present approach is a new and sensitive method to characterize the profile of soluble Aβ in conditioned media and biological fluids. Furthermore, it allows direct measurement of each individual peptide in a peptide mixture and provides comprehensive information on the identity and concentration of Aβ and Aβ variants.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the matrix-assisted laser desorption ionization mass spectrometry taught by Jimenez or Wang in the methods of Tellerova, Shibata, Nagase, Mabuchi, Leber, Kodama, Klosse or Charpentier because of the sensitivity and ability to profile and directly measure each peptide present as taught by Jimenez and Wang.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to disease analysis based on peptide/protein profiles or markers.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (703) 308-3989. The examiner's schedule is variable between the hours of about 5:30 AM to about 5:00 PM on Monday through Thursday and alternate Fridays.

For communication by fax to the organization where this application or proceeding is assigned, (703) 305-7719 may be used for official, unofficial or draft papers. When using this number a call to alert the examiner would be appreciated. Numbers for faxing official papers are 703-872-9310 (before finals), 703-872-9311 (after-final), 703-305-7718, 703-305-5408 and 703-305-5433. The above fax numbers will generally allow the papers to be forwarded to the examiner in a timely manner.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Arlen Soderquist

December 11, 2002

ARLEN SODERQUIST
PRIMARY EXAMINER